

REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Office Action mailed on December 27, 2002. Claims 60-62 have been withdrawn from consideration. Claims 68-82 have been added. Claims 1, 4, 7-19, 30, and 63-82 are pending. Claims 1, 4, 7-19, 30, and 63-67 have been rejected.

Applicants acknowledge with appreciation that the rejection under 35 U.S.C. §112, 2nd paragraph and the rejection under 35 U.S.C. §103 have been withdrawn

This amendment is to expedite prosecution and should not be construed as acquiescence in any ground of rejection. Applicants reserve the right to prosecute the originally filed claims, and any other claims supported by the specification, in the future. The comments in the Office action are now addressed in turn.

Withdrawal from Consideration

The Office has withdrawn new claims 60-62 from consideration as they are drawn allegedly to subject matter that is not originally presented. Applicants respectfully traverse.

In order for this withdrawal from consideration to be proper, the claim groups identified must be independent or distinct from one another. In addition, examining all claim groups in a single application must present a serious burden on the Examiner.

Applicants respectfully maintain that it would not place an undue burden on the Examiner to include Claims 60-62 with the other pending claims in this case. Applicants respectfully request that Claims 60-62 be rejoined with Claims 1, 4, 7-19, 30, and 63-67.

Rejections under 35 U.S.C. §112

Claim 12 has been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and claim the invention. Applicants respectfully traverse this rejection.

The Office has expressed concern regarding the antecedent basis of Claim 12. Applicants have amended the claim herein to address the Examiner's concern. Applicants request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-4, 7-19, 30, and 63-67 have been rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Comgenex and Maybridge in view of Aono. Applicants respectfully traverse this rejection.

The Office has cited Comgenex and Maybridge for their description of compounds having R₄ as “dimethylamino-propyl”, “dimethylamino-ethyl” (or “substituted lower alkyl”), and “alkylheteroaryl”. Aono is cited for its description of a genus of compounds that inhibit cell growth and have antitumor activity. The Examiner argues that Aono would have provided sufficient motivation for one skilled in the art to use some of the claimed compounds in the treatment of cellular proliferative disease. Applicants must respectfully disagree.

As a preliminary matter, Applicants assert that the Examiner has not established *prima facie* obviousness. A *prima facie* case of obviousness requires the Examiner to cite to a reference which (a) discloses all the elements of the claimed invention, (b) suggests or motivates one of skill in the art to combine or modify those elements to yield the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out (See, e.g., *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); and *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988)). Failure to establish **any one** of these three requirements precludes a finding of a *prima facie* case and, without more, entitles Applicant to allowance of the claims at issue. As stated in *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988):

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure.

Applicants assert that cited references, either alone or in combination, do not teach or suggest the presently claimed invention.

The present invention is directed to methods of utilizing a novel class of compounds having a core quinazolinone structure that are modulators of mitotic kinesins, and more particularly, modulators of the mitotic kinesin KSP. Applicants have amended the claims herein to focus on a particular embodiment of the present invention, namely, methods of treating cellular proliferative diseases comprising the administration of a quinazolinone amides of formula 1(a). The compounds used in the claimed methods have been defined by quite specific substituents at the various R groups. In addition, each of the compounds used in the claimed

methods have a sidechain that is a tertiary amide, i.e., the amide nitrogen does not bear a hydrogen group.

As is detailed in the Specification at Examples 4-8 and at pages 47-48 and Figure 3, compounds within these classes have been shown to inhibit cell proliferation with GI₅₀ values well within the range of anti-proliferative agents used in the clinic. These compounds can be used, for example, to inhibit human KSP; to treat diseases of proliferating cells; to develop inhibitors and modulators of KSP; and the like.

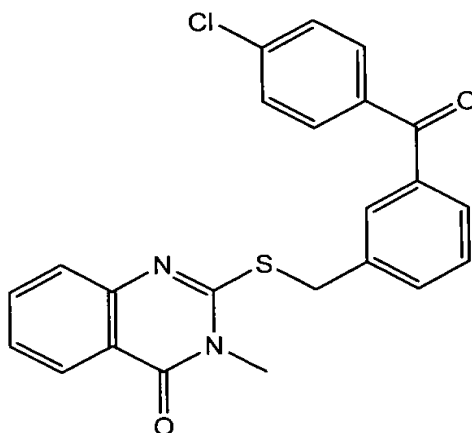
Aono describes compound of the formula A-Z-Ar¹-(CO)-Ar². In some embodiments, the substituent A is a condensed pyrimidinone, for example a quinazolinone ring. However, Aono indicates that the quinazolinone (i.e., substituent A) must be coupled to -Z-Ar¹-(CO)-Ar² wherein Z is a divalent group or a salt thereof; and Ar¹ and Ar² are independently an optionally substituted ring. More specifically, Z is a

group connecting the condensed pyrimidinone or condensed pyridazinone ring to the ring (Ar¹) and contains 1 to 5 (preferably 1 to 3) atoms selected from carbon, nitrogen, oxygen and sulfur. The group includes a divalent aliphatic group (e.g. straight-chain or branched aliphatic group consisting of 1 to 6 carbon atoms) which contains --NH--, --O-- or --S-- in the suitable positions.

See, Aono at Column 15, emphasis added.

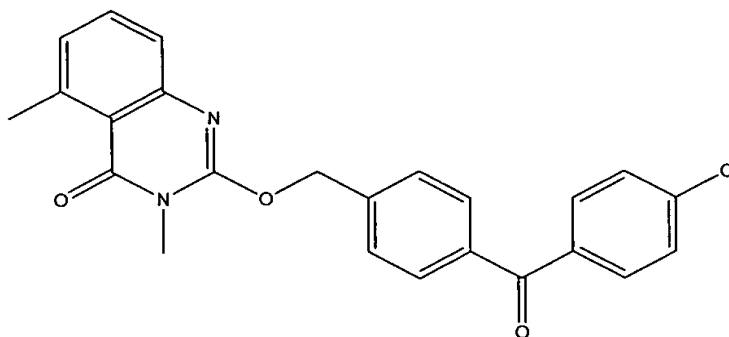
Aono provides the following examples of compounds of the formula A-Z-Ar¹-(CO)-Ar².

- (1) Z is straight-chain or branched aliphatic group consisting of 1 to 6 carbon atoms which contains a --S-- group. See, e.g., Example 3 drawn to 2-(3-(4-chlorobenzoyl)benzyl)thio-3-methyl-4(3H)-quinazolinone

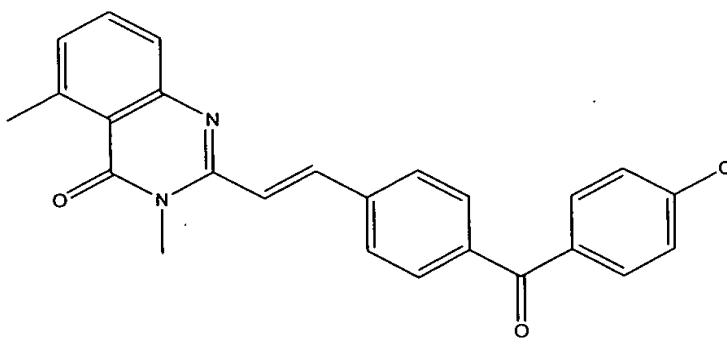


See, also, Examples 1, 2, 4, 41, 42, 43, 44, 45, 113, 114, 115, 116, 117, 118, 119, 120, 138, 139-142, 143, 144, 145, 150, 151, 167, 168, 171, 173, 174-176, 179-180, 182-184, and the like.

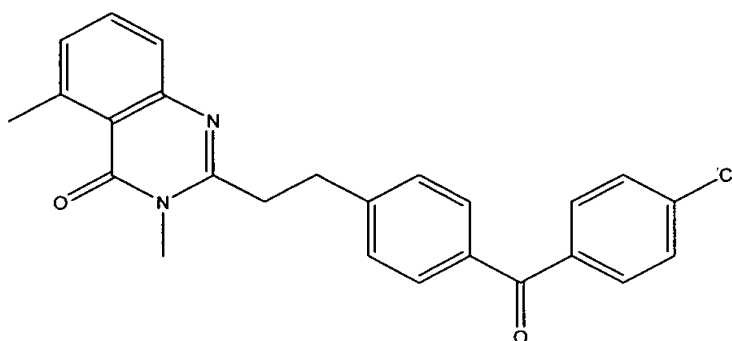
- (2) Z is a straight-chain or branched aliphatic group consisting of 1 to 6 carbon atoms which contains a --O-- group. See, e.g., Example 134 – 2-(4-(4-Chlorobenzoyl)benzyloxy)-3,5-dimethyl-4(3H)-quinazolinone or Example 135.



- (3) Z is a C₁₋₆ alkylene or C₂₋₆ alkylenylene. See, Example 261 which is drawn to 2-(2-(4-(4-Chlorobenzoyl)phenyl)vinyl)-3,5-dimethyl-4(3H)-quinazolinone



See, also, Example 262 which is drawn to 2-(2-(4-(4-chlorobenzoyl)phenyl)ethyl)-3,5-dimethyl-4(3H)-quinazolinone.



As the Examiner will note from the description of Z and the compounds shown above, Aono describes compounds that have an --S--, --O--, --NH--, or alkylene or alkenylene group attaching a quinazolinone ring to an aromatic ring (which is, in turn, coupled to another aromatic ring through a carbonyl functionality). Aono does not describe an amide linkage between the aromatic ring and the quinazolinone ring system.

In contrast to Aono, the methods claimed herein are drawn to methods of treating cellular proliferative diseases comprising the administration of a *quinazolinone amides* of formula 1(a). Applicants respectfully maintain that Aono does not teach or suggest that the compounds used in the claimed methods – compounds that have an *amide* side chain – would be useful in the treatment of cellular proliferative disease. Applicants respectfully maintain that there is simply no suggestion in the cited references that a quinazolinone having an amide side chain, as claimed herein, would be useful for the treatment of cellular proliferative disease. Thus, there is nothing in the cited prior art that would provide one of ordinary skill in the art with the knowledge necessary to develop the claimed inventions.

As the reference does not teach the presently claimed invention, Applicants assert that by suggesting that the cited art may be used to produce the methods of the presently claimed invention, the Examiner presents, in essence, an "obvious to experiment" or "obvious to try" standard for obviousness. The "obvious to try" standard has been thoroughly discredited. Indeed, an obviousness rejection is inappropriate, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful" (quoting *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 [Fed. Cir. 1988], *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 10 USPQ2d 1843, 1845 [Fed. Cir. 1989]).

There is no teaching in either of the cited references regarding methods to treat cellular proliferative disease using quinazolinone amides as claimed herein. Thus, there is simply

nothing in the cited prior art that would provide one of ordinary skill in the art with the knowledge necessary to develop methods (*i.e.*, with the parameters and elements necessary to successfully conduct the presently claimed methods).

Applicants respectfully submit that the claimed invention is not obvious from the cited references. Applicants request that the rejection be withdrawn.

Conclusion

The Applicants respectfully maintain that all pending claims are in condition for allowance. Therefore, the Applicants respectfully request a Notice of Allowance for this Application from the Examiner. Should any unresolved issues remain, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

BEYER WEAVER & THOMAS, LLP

A handwritten signature in black ink, appearing to read 'Lauren L. Stevens', with a long horizontal flourish extending to the right.

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